

REMARKS/ ARGUMENTS

Applicant has carefully studied the final Examiner's Action mailed August 26, 2008, having a shortened statutory period for response set to expire November 26, 2008. The amendment appearing above and these explanatory remarks are believed to be fully responsive to the Action. Accordingly, this important patent application is now believed to be in condition for allowance.

Claim Rejections - 35 U.S.C. § 112

Office has rejected claims 1-5, 7, 17, and 20 under 35 U.S.C. § 112, first paragraph, contending that the specification does not enable preventing the side effects. The Office also found that the specification is "enabling for treatment of side effects of NSAIDs and providing tissue protection[.]"but that the invention is not commensurate with the scope of the claims.¹ Applicant has amended the claims to claim "preventing, reducing and reversing the toxic gastrointestinal effects of anti-inflammatory drugs and enhancing the beneficial effects of anti-inflammatory drugs[.]"

To determine whether a disclosure adequately enables an invention, a series of factors have been established, including the breadth of claims, nature of the invention, state of prior art, relative skill in the art, predictability in the art, the amount of direction or guidance, presence of working examples, and amount of experimentation needed.² 35 U.S.C. § 112 is satisfied if "the specification contains within it a *comnotation* of how to use" the invention or the use is known in the art.³

Breadth of Claims

The Office contends the claims are overbroad, as the claims cover preventing side effects of anti-inflammatory drugs, such as kidney failure, ulcers, fluid retention, rash decreased appetite, headache, and drowsiness.⁴ Further, side effects of non-steroidal anti-inflammatory drugs (NSAIDs) differ from steroidal anti-inflammatory drugs (SAIDs).⁵ Office concludes by stating the invention may or may not address all the side effects.

¹ Page 2 of the final Office Action, dated Aug. 26, 2008.

² *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

³ MPEP 2164.01(c). (Emphasis added).

⁴ Page 3 of the final Office Action, dated Aug. 26, 2008.

⁵ *Id.*

Applicant has amended claim 1 to provide “preventing, reducing and reversing the toxic gastrointestinal effects of anti-inflammatory drugs [.]” Claim 1 is thus limited to specific effects of the anti-inflammatory drugs.

NSAID effects are generally mediated through cyclooxygenase (COX) enzyme inhibition.⁶ The inhibition of COX causes reduced eicosanoid synthesis.⁷ Nonselective COX inhibition causes adverse effects, including gastrointestinal (GI) problems like gastroduodenal ulcers and gastrointestinal bleeding.⁸ Use of selective COX-2 inhibitors has been shown to alleviate GI side effects, but increases adverse cardiovascular events.⁹ Like NSAIDs, SAIDs has been shown to also reduce inflammatory response through COX inhibition and eicosanoid formation inhibition.¹⁰ The anti-inflammatory effects of NSAIDs and SAIDs rely on the same pathway, at least partly, and therefore the side effects of both NSAIDs and SAIDs may be prevented and treated by targeting such common pathways between the NSAIDs and SAIDs.

The specification shows administering an MAO-B inhibitor prior to a NSAID provided protection to gastrointestinal mucous after one pretreatment and reverses gastrointestinal lesions by one week pretreatment.¹¹ As anti-inflammatory effects of NSAIDs and SAIDs rely on the same pathway, at least partly, the disclosure provides disclosure on treating both NSAID and SAID gastrointestinal toxic effects, and the claims are enabled by the disclosure.

Nature of the Invention

The Office found the nature of the invention complex, as “it encompasses the actual prevention of an undisclosed side effect of an anti-inflammatory medication.”¹² As amended, the claimed invention is drawn to “preventing, reducing and reversing the toxic gastrointestinal effects of anti-inflammatory drugs[.]” Preventative and reductive treatments for anti-

⁶ Page 2 of the Application. J. Masferrer, K. Seibert, B. Zweifel, P. Needleman, “Endogenous Glucocorticoids Regulate an Inducible Cyclooxygenase Enzyme,” *Proc. Nat. Acad. Sci.*, 1992, 89, 3917-3921, page 3919, column 2.

⁷ *Id.*

⁸ Unknown author, “Balancing Cardiovascular Risks and Gastrointestinal Outcomes in NSAID Users: A Report from a Symposium held During the American College of Gastroenterology 71st Annual Meeting and Postgraduate Course,” *Gastroent. & Hepat.*, Mar. 2007, 3:3, 4-13, page 4, column 1.

⁹ *Id.* at page 4, column 2; page 6, column 2.

¹⁰ J. Masferrer, K. Seibert, B. Zweifel, P. Needleman, “Endogenous Glucocorticoids Regulate an Inducible Cyclooxygenase Enzyme,” *Proc. Nat. Acad. Sci.*, 1992, 89, 3917-3921, page 3917, columns 1-2; page 3919, column 2; page 3920, columns 1-2.

¹¹ Example 5, pages 22-23; table 3, page 25 of the Application.

¹² Page 4 of the final Office Action, dated Aug. 26, 2008.

inflammatory drugs, such as synthetic prostagladins, proton pump inhibitors (PPI)¹³, and vitamin C¹⁴, have been tested for effectiveness in treating and preventing anti-inflammatory side effects. Therefore, the nature of the invention, while complex, is not outside the understanding of one skilled in the art.

State of the Prior Art

The Office noted the state of the prior art is “relatively high” for treating side effects of anti-inflammatory drugs, but is underdeveloped for preventing side effects.¹⁵

The specification provides examples of MAO inhibitors preventing anti-inflammatory drug side effect damage. For example, administering an MAO-B inhibitor prior to a NSAID provided protection to gastrointestinal mucous after one pretreatment and reversed gastrointestinal lesions by one week pretreatment.¹⁶ In similar experiments conducted over 7 days, pretreatment with L-deprenyl or propargylamine prevented formation of gastric lesions and reversed lesions.¹⁷

Relative Skill in the Art

Office states that the level of ordinary skill in the art is “that of a physician.”¹⁸ The level of skill in the art is determined by determining the subject matter at the time of filing.¹⁹ The current invention is classified as “Art Unit” 1614, comprising drugs and “bio-affecting” compositions.²⁰ The pharmaceutical, medicinal, and scientific arts are considered highly skilled arts. As such, the specification does not need to specify limitations if the prior art or knowledge of similar physiological or biological activity in the biotech and medical sciences.²¹

Predictability in the Art

The Office found a lack of “significant guidance from the specification or prior art with regard to the actual **prevention** of side effects[.]”²² Applicant respectfully points out examples are disclosed in the application that show the effectiveness of L-deprenyl and propargylamine

¹³ D. Graham, et al., “Ulcer Prevention in Long-Term Users of Nonsteroidal Anti-inflammatory Drugs,” Arch. Intern. Med., Jan. 28, 2002; 162: 196-175, pages 169, 173-174.

¹⁴ J. Becker, W. Domschke, T. Pohl, “Current Approaches to Prevent NSAID-Induced Gastropathy- COX Selectivity and Beyond,” Br. J. Pharmacol., Dec. 2004; 58(6):587-600, abstract.

¹⁵ Page 4 of the final Office Action, dated Aug. 26, 2008.

¹⁶ Example 5, pages 22-23; table 3, page 25 of the Application.

¹⁷ Id.

¹⁸ Page 4 of the final Office Action, dated Aug. 26, 2008.

¹⁹ MPEP 2164.05(b).

²⁰ http://www.uspto.gov/web/offices/opc/caau/1614_1754.htm, Definitions of art units.

²¹ MPEP 2164.01(c).

pretreatment in preventing formation of gastric lesions after acute treatment.²³ and prevented formation of gastric lesions and reversed lesions after continued treatment.²⁴ For example, administering 5 mg/kg deprenyl prior to a NSAID result in inhibition of leukocyte activation and adhesion,²⁵ and administering 0.5 mg/ kg propargylamine (MAO inhibitor from example 1) prior to a NSAID provided protection to gastrointestinal mucous after one pretreatment and reversed gastrointestinal lesions by one week pretreatment.²⁶ In similar experiments conducted over 7 days, pretreatment with l-deprenyl or propargylamine prevented formation of gastric lesions and reversed lesions.²⁷ Therefore, any questions as to the predictability of the invention have been addressed by the specification.

Amount of Direction or Guidance

The Office contends the guidance provided in the specification is minimal as to the medications used and side effects prevented.²⁸ The specification provides that NSAID gastropathology is a result of gastric microcirculation²⁹ and that MAO inhibitors may be administered at 0.1 to 10 times the NSAID dose of 0.1-500 mg/kg.³⁰ The specification further provides guidance as to the timing³¹ and amount of MAO inhibitor to use to effectively prevent anti-inflammatory side effects.³² For example, l-deprenyl shows a reduction in gastric lesion damage at 100 mg/kg and at 200 mg/kg; 21-40% and 1-20% of lesions in mice treated only with anti-inflammatory, respectively.³³ The specification also includes working examples of the invention in reducing gastric ulceration, illustrating that the administration of MAO inhibitor provides a protective effect for cells.³⁴ Therefore, the specification provides both direction and guidance as to the timing and dosage of MAO inhibitor to use to effectively prevent anti-inflammatory side effects.

²² Page 5 of the final Office Action, dated Aug. 26, 2008 (Emphasis in original).

²³ *Id.* at page 23; table 3.

²⁴ *Id.*

²⁵ Example 3, pages 21-22 of the Application.

²⁶ Example 5, pages 22-23; table 3, page 25 of the Application.

²⁷ *Id.*

²⁸ Page 5 of the final Office Action, dated Aug. 26, 2008.

²⁹ Page 4 of the Application.

³⁰ Page 19 of the Application.

³¹ Page 23 of the Application ("MAO inhibitor was administered by oral gavage immediately prior to administration of NSAID"; "[F]ollowing 8 hours after NSAID dosing the animals were provided food and water []. They were treated daily with oral gavage of MAO inhibitor for 7 days.").

³² Pages 22-23; 25, table 3 of the Application.

³³ Page 25, table 3 of the Application.

Amount of Experimentation Needed

The Office states a skilled artisan must envision a combination of pharmaceutical carrier, dosage, duration of treatment, route of administration, and determine an animal model before the invention may be practiced.³⁵ The specification provides the MAO inhibitor may be administered numerous ways, including orally, parentally, intravenously, intraduodenally, intracutaneously, and intranasally.³⁶ The specification also teaches a method of chemically linking an MAO inhibitor to a NSAID³⁷ and teaches an unlinked MAO inhibitor may be administered prior to anti-inflammatory drug treatment.³⁸

The Office found a skilled artisan must test the preventive effects of MAO inhibitors on NSAID side effects.³⁹ However, L-deprenyl and propargylamine pretreatment was shown effective in preventing formation of gastric lesions after acute treatment,⁴⁰ and prevented formation of gastric lesions and reversed lesions after continued treatment.⁴¹ Using 5 mg/kg deprenyl or 0.5 mg/kg propargylamine (MAO inhibitor from example 1).

“Enablement is not precluded by the necessity for some experimentation *such as routine screening*.”⁴² Varying the timing for treatment administration and/or the dosage of anti-inflammatory and MAO inhibitor is essentially a drug screening process. According to *Wands*, screening is within the routine practice of the medicinal and scientific arts.⁴³ Based on the prior work performed in the art, the level of skill in the art, and the disclosure, the invention is adequately described for prevention, reduction, and reversion of the side effects of anti-inflammatory drugs.

Presence of Working Examples

The specification shows administering an MAO-B inhibitor prior to a NSAID provided protection to gastrointestinal mucous after one pretreatment and reverses gastrointestinal lesions

³⁴ Page 25, table 3 of the Application (Providing lesion reduction at provided dosages for L-deprenyl and propargylamine).

³⁵ Page 5 of the final Office Action, dated Aug. 26, 2008.

³⁶ Page 19 of the Application.

³⁷ Example 1, pages 20-21 of the Application.

³⁸ Example 5, pages 22-23 of the Application.

³⁹ Page 5 of the final Office Action, dated Aug. 26, 2008.

⁴⁰ Example 3, pages 21-22 of the Application; Example 5, pages 22-23; table 3, page 25 of the Application.

⁴¹ *Id.*

⁴² *In re Wands*, 858 F.2d at 736-737. (Emphasis added).

⁴³ See generally, *In re Wands*, 858 F.2d at 739.

by one week pretreatment.⁴⁴ may be prevented and treated by targeting such common pathways between the NSAIDs and SAIDs. In similar experiments conducted over 7 days, pretreatment with L-deprenyl or propargylamine prevented formation of gastric lesions and reversed lesions.⁴⁵

The application also discloses MAO inhibitor tests on C-reactive protein, which is elevated in obesity and diabetes and a possible side effect of hormone therapy.⁴⁶ Blood samples were taken from human subjects, followed by administration of L-deprenyl.⁴⁷ After seven days, blood CRP levels were reduced 30% in L-deprenyl-treated individuals.⁴⁸

Not every embodiment or procedure to practice the invention need be disclosed for the invention to be enabled.⁴⁹ The application discloses that MAO inhibitors L-deprenyl and propargylamine effectively prevent formation of gastric lesions and reverse lesion progression during prolonged treatment, as seen in table 3.⁵⁰ The claims do not require all side effects of each drug be prevented, but rather for enablement the invention must prevent or treat at least one side effect of the drugs. L-deprenyl and propargylamine treatment is shown effective in preventing and reducing NSAID side effects. SAIDs act through the same pathway as NSAIDs, by inhibiting COX, to produce an anti-inflammatory effect. Though NSAIDs and SAIDs have different side effects, both anti-inflammatory treatments utilize COX-dependent pathways. As such, the application discloses at least one example of preventing the side effects of NSAIDs and SAIDs. Therefore, NSAIDs and SAIDs may be effectively treated by compounds that target such similar pathways and the claims are consistent with the scope of the disclosure.

A specification does not require working examples, but may utilize prophetic examples to describe the invention based on “predicted results.”⁵¹ The specification does include working examples of the invention in reducing platelet activation and reducing gastric ulceration.⁵² Cardiovascular events, caused by anti-inflammatory treatment, develop due to the prothrombic activity of the drugs, causing platelet coagulation and resulting in cardiovascular events like congestive heart failure, stroke, vascular death, and myocardial infarction.⁵³ Leukocyte

⁴⁴ Example 5, pages 22-23; table 3, page 25 of the Application.

⁴⁵ *Id.*

⁴⁶ *Id.* at page 24.

⁴⁷ *Id.*

⁴⁸ *Id.*

⁴⁹ MPEP2164.08

⁵⁰ *Id.* at page 23; table 3.

⁵¹ MPEP 2164.02. Citing *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987).

⁵² Examples 3 and 5, pages 21-23 of the Application.

⁵³ *Id.* at page 5-6.

activation and adhesion is known in the art,⁵⁴ and pretreatment of L-deprenyl (5 mg/kg) inhibited leukocyte activation induced by TNF- α ,⁵⁵ thereby preventing cardiovascular events caused by anti-inflammatory drugs. Additionally, the specification discloses L-deprenyl and propargylamine reduces and prevents gastric lesions,⁵⁶ commonly caused by anti-inflammatory drug treatment. Thus, the specification illustrates that the treatment of an MAO inhibitor effectively prevents, reduces, and reverses the effects of anti-inflammatory drugs.

35 U.S.C. § 112 is satisfied if “the specification contains within it a *connotation* of how to use” the invention or the use is known in the art.⁵⁷ Office bears the initial burden to show the specification does not enable the claimed invention. The medicinal and scientific arts are highly skilled arts, as discussed *supra*. The specification provides guidance as to the timing and dosage of MAO inhibitor, as refers to the prior art (PDR) for calculations on patient dosages. The specification does include working examples of the invention in gastrointestinal ulceration prevention and reduction/ reversal, as well as prevention of cardiovascular events. As such, based on the prior art, skill of the ordinary artisan, and disclosure, the invention is adequately described to allow a skilled artisan to use the invention for treatment for preventing, reducing and reversing the toxic effects of anti-inflammatory drugs. The *Wands* factors indicate the invention may be performed without undue experimentation, as discussed *supra*. Accordingly, it is respectfully requested that the rejection of claims 1-5, 7, and 20 be withdrawn by the Office.

Claim Rejections - 35 U.S.C. § 112

Office has rejected claims 1-5, 7, 17, and 20 under 35 U.S.C § 112, second paragraph. Applicant gratefully acknowledges the concerns enunciated by Examiner Jagoe and has amended the claims to address the Examiner. Accordingly, Applicant respectfully requests withdraw of the 35 U.S.C § 112, second paragraph rejection of claims 1-5, 7, 17, and 20.

Claim Rejections - 35 U.S.C. § 103

Claims 1-5, 7, 17, and 20 stand rejected under 35 U.S.C. § 103(a) in view of Glavin, et al. (Neurosci. Ltrs., 1986) and Lianping, et al. (Dig. Disease Sci., 1990). The Office found that Glavin teaches an association between duodenal ulcer occurrence and dopamine deficiency.⁵⁸

⁵⁴ See, T. Thomas, J. Rhodin, L. Clark, A. Garces, “Progestin Initiate Adverse Events of Menopausal Estrogen Therapy,” *Climacteric*, Dec. 2003; 6(4):293-301.

⁵⁵ Example 3, page 21 of the Application.

⁵⁶ Example 5, page 23; table 3, page 25 of the Application.

⁵⁷ MPEP 2164.01(c). (Emphasis added).

⁵⁸ Page 10 of the final Office Action, dated Aug. 26, 2008.

The Office also noted disorders with excessive dopamine activity rarely associate with duodenal ulcers (pathology), and pretreatment with L-deprenyl prevented ulcers in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated rats.⁵⁹ Office went on to find Lianping teaches MAO inhibitors inhibit gastrin release, protecting mucosa from stress-induced ulceration from gastrin release.⁶⁰ The Office noted that neither Glavin⁶¹ nor Lianping⁶² “teach a method of preventing, reducing, and reversing the toxic effects of anti-inflammatory drugs[.]” but that it was obvious to employ MAO inhibitors to prevent the toxic effects of anti-inflammatory agents because Glavin teaches l-deprenyl prevents ulceration in dopamine depleted rats and Lianping teaches MAO inhibition protects from stress-induced gastrin ulceration, thus disclosing protective gastrointestinal effects.⁶³

Applicant respectfully traverses the rejection because one or more elements are missing from the combination of Glavin and Lianping. A *prima facie* case of obviousness must be made to support a rejection under 35 USC §103(a).⁶⁴ Glavin discloses that dopamine effects duodenal ulceration, and such duodenal ulceration may be prevented by administration of pargyline or L-deprenyl.⁶⁵ Lianping likewise teaches that depleted levels of central nervous system dopamine or norepinephrine increase gastric output and result gastrointestinal mucosal injury, which are attenuated by pretreatment with l-deprenyl.⁶⁶ In determining obviousness, the invention must be considered in its entirety.⁶⁷ To consider the invention as a whole, all claim limitations must be considered in analyzing a claim for obviousness.⁶⁸ Claim 1 has been amended⁶⁹ to provide

A method of preventing, reducing and reversing the toxic gastrointestinal effects of anti-inflammatory drugs and enhancing the beneficial effects of anti-inflammatory drugs, comprising:
administering to a subject an effective amount of MAO inhibitor;

⁵⁹ *Id.*

⁶⁰ *Id.* at page 11.

⁶¹ *Id.* at page 10.

⁶² *Id.* at page 11.

⁶³ *Id.*

⁶⁴ MPEP 2143 - “The legal concept of *prima facie* obviousness is a procedural tool of examination which applies broadly to all arts. ... The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness.”

⁶⁵ G. Glavin, A. Dugani, C. Pinsky, “L-Deprenyl Attenuates Stress Ulcer Formation in Rats,” *Neurosci. Ltrs.* 1986; 70:379-381, page 380-381.

⁶⁶ Lianping Xing, J. Seaton, G. Kauffman, “Monoamine Oxidase B Inhibition Reduces Gastric Mucosal Blood Flow, Basal Acid Secretion, and Cold Water Restrain-Induced Gastric Mucosal Injury in Rats,” *Digestive Dis. And Sci.*, Jan. 1990; 35(1):61-65, page 64, column 1; page 63, column 2; page 63, table 3.

⁶⁷ See, MPEP 2141.02(I).

⁶⁸ *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See also, MPEP 2141.02(I).

⁶⁹ See, page 2 of Amendment B.

wherein the anti-inflammatory drug and MAO inhibitor are chemically linked, physically mixed or administered separately.

Glavin and Lianping studied only stress induced ulcers caused by cold exposure. The authors suggest that this is mediated by brain dopamine, as noted by the Office.⁷⁰ Moreover, Lianping expressly limited its teachings to determining protection via antisecretory effects of MAO-B inhibition.⁷¹ Claim 1 is limited to NSAID-induced gastric injury, which is caused by direct effect of the drug on gastrointestinal mucosa. While the combination of Lianping and Glavin may show l-deprenyl is effective in protecting the gastrointestinal tract from stress-induced injury, any such teachings, in combination, do not address NSAID-associated gastrointestinal injury. The Office noted that neither Glavin nor Lianping “teach a method of preventing, reducing, and reversing the toxic effects of anti-inflammatory drugs[.]”⁷² thus the combination of the two references “do not teach a method of preventing, reducing, and reversing the toxic effects of anti-inflammatory drugs[.]”⁷³ Brain dopamine mechanisms are not involved in NSAID toxicity, but rather decreased prostaglandin E2 synthesis in the gastrointestinal mucosa and decreased gastrointestinal mucosal blood flow are believed to cause much of the NSAID-induced gastric injury.⁷⁴ The administration of MAO inhibitors has numerous localized effects, including preventing apoptosis, inhibiting oxidative stress, stimulating expression and activity of antioxidant enzymes, increasing mucosal blood flow, stimulating nitric oxide synthase, and inhibiting platelet activation and thrombic activity,⁷⁵ which act to prevent, reduce, and reverse the effects of anti-inflammatory drugs. Therefore, the proposed combination of Glavin and Lianping fail to teach the invention as claimed by claim 1.

⁷⁰ Page 10 of the final Office Action, dated Aug. 26, 2008 (“disorders characterized by excess dopamine activity ... rarely associated with duodenal pathology.”);

⁷¹ *Id.* at page 64, column 1 (“These studies were not designed to determine whether protection of the gastric mucosa is related to any effect of the MAO-B inhibitor other than the antisecretory effect.”).

⁷² Page 10, last paragraph of the final Office Action, dated Aug. 26, 2008; page 11, second paragraph of the final Office Action, dated Aug. 26, 2008.

⁷³ *Id.*

⁷⁴ Wallace, J.L., Building a better aspirin: gaseous solutions to a century old problem. *Br J Pharmacol.* 2007, 152: 421-428, 423; Nishizawa T., et al., Reduced conscious blood flow in the stomach during non-steroidal anti-inflammatory drugs administration assessed by flash echo imaging. *Scand J Gastroenterol.* Sep 2007, 42(9): 1040-4; Funatsu T. Mucosal acid causes gastric mucosal microcirculatory disturbance in nonsteroidal anti-inflammatory drug-treated rats. *Eur J Pharmacol.* Jan 5 2007, 554(1): 53-9 ; Kawano S. J., Tsuji, S., Role of mucosal blood flow: A conceptional review in gastric mucosal injury and protection. *J Gastroenterol Hepatol.* Mar 2000, 15:D1-6.

⁷⁵ *Id.*

"All words in a claim must be considered in judging the patentability of that claim against the prior art."⁷⁶ The question is not whether the elements of the invention would be obvious, but rather whether the invention as a whole would have been obvious.⁷⁷ The combination of Glavin and Lianping fail to obviate the present invention because the combined references fail to disclose the elements of the claimed invention. Therefore, a *prima facie* case of obviousness has not been established against the claimed invention, as amended. Accordingly, Applicant respectfully requests the 35 U.S.C. § 103(a) rejection of claims 1-5, 7, 17 and 20 be withdrawn.

Conclusion

Applicant respectfully requests that a timely Notice of Allowance be issued in this case. If the Office is not fully persuaded as to the merits of Applicant's position, or if an Examiner's Amendment would place the pending claims in condition for allowance, a telephone call to the undersigned at (813) 925-8505 is requested.

Very respectfully,

SMITH & HOPEN

/thomas e toner/

By: _____

Dated: November 26, 2008
Customer No. 21,901

Thomas E Toner
Reg. No. 57,422
180 Pine Avenue North
Oldsmar, Florida 34677
Attorneys for Applicant

⁷⁶ MPEP 2143.03 citing *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

⁷⁷ See MPEP 2142.02 – Differences Between the Prior Art and the Claimed Invention – "In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983)."

CERTIFICATE OF ELECTRONIC TRANSMISSION

(37 C.F.R. 2.190 (b))

I HEREBY CERTIFY that this correspondence is being electronically transmitted to the Patent and Trademark Office through EFS Web on November 26, 2008.

Date: November 26, 2008

/erica gossage/

Erica Gossage